AL/CF-TP-1995-0028

EFFECTS OF MELATONIN ON DIURNAL MOOD

Paul S. Stoner, Jr., Lieutenant Colonel, USAF

School of Aerospace Medicine
2513 Kennedy Circle
Brooks Air Force Base, TX 78235-5123

Jonathan French
Rodney Hughes
Jeffrey Whitmore

CREW SYSTEMS DIRECTORATE
Crew Technology Division
2504 Gillingham Drive, Suite 25
Brooks Air Force Base, TX 78235-5104

March 1996

Final Technical Paper for Period January 1992-January 1993

AIR FORCE MATERIEL COMMAND
BROOKS AIR FORCE BASE, TEXAS

ARMSTRONG LABORATORY

NOTICES

When Government drawings, specifications, or other data are used for any purpose other than in connection with a definitely Government-related procurement, the United States Government incurs no responsibility or any obligation whatsoever. The fact that the Government may have formulated or in any way supplied the said drawings, specifications, or other data, is not to be regarded by implication, or otherwise in any manner construed, as licensing the holder or any other person or corporation; or as conveying any rights or permission to manufacture, use or sell any patented invention that may in any way be related thereto.

The voluntary, fully informed consent of the subjects used in this research was obtained as required by AFI 40-402.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

Jon French

JONATHAN FRENCH, Ph.D.
Project Scientist

Patricia A Boll

PATRICIA A. BOLL
Acting Chief, Sustained Operations Branch

James P Dixon

JAMES P. DIXON, Colonel, USAF, BSC
Chief, Crew Technology Division

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	March 1996	Final Report Jan 92 - Jan 93

4. TITLE AND SUBTITLE
Effects of Melatonin on Diurnal Mood

5. FUNDING NUMBERS
PE - 62202F
PR - 7930
TA - 19
WU - 01

6. AUTHOR(S)
Paul S. Stoner, Jr., Jonathan French, Rodney J. Hughes, Jeffrey N. Whitmore

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Armstrong Laboratory (AFMC)
Crew Systems Directorate
2504 Gillingham Dr, Ste 25
Brooks Air Force Base, TX 78235-5104

8. PERFORMING ORGANIZATION REPORT NUMBER
AL/CF-TP-1995-0028

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Armstrong Laboratory (AFMC)
Crew Systems Directorate
2504 Gillingham Dr, Ste 25
Brooks Air Force Base, TX 78235-5104

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES
Armstrong Laboratory Project Scientist: Dr Jonathan French, (210) 536-3464

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

As a substance produced nocturnally by the pineal gland, melatonin may have utility in promoting sleep during diurnal or other unusual sleep periods. Oral doses (100 mg and 10 mg) of melatonin were used to evaluate effects on diurnal mood and oral temperature. The six subjects in the experiment were male volunteers (range 20-42 years old). Oral temperature, plasma and salivary melatonin samples were obtained every 2 hours beginning at 0800 until 1700. A significant correlation ($r = 0.74$) occurred between plasma and salivary melatonin samples. Temperature effects, subjective fatigue and confusion scores were increased by the 100 mg dose within 3-4 hours after dosing. Salivary levels of melatonin may be used as a non-invasive measure of plasma melatonin. As a substance produced endogenously, melatonin may make a useful non-addictive soporific devoid of typical sedative side effects.

14. SUBJECT TERMS	15. NUMBER OF PAGES
Melatonin Serum Saliva Mood Fatigue	30
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	UL

CONTENTS

LIST OF FIGURES

EFFECTS OF MELATONIN ON DIURNAL MOOD

SUMMARY

The pineal hormone melatonin influences the human circadian timing system by signalling the nocturnal phase. Melatonin's effect on diurnal fatigue in humans has been well documented. The ability of melatonin to influence other mood states out of it's normal nocturnal circadian phase was evaluated. Effects comparing serum and salivary levels and on oral temperature were also determined. The study was conducted at the Sustained Operations Branch of Armstrong Laboratory at Brooks Air Force Base during July and August of 1992. The 6 male subjects were unpaid volunteers. Either melatonin (100 mg and 10 mg) or placebo was administered in a randomized and within groups design, orally, in gelatin capsules at about 0915, on three successive Saturdays, after a normal nights sleep. Salivary melatonin was significantly correlated with plasma levels providing a simpler means to assess melatonin. There was a dose dependent rise in melatonin levels. The 100 mg dose of melatonin produced effects on fatigue and confusion mood dynamics. An interaction of melatonin with time occurred in oral temperature. Melatonin seems to be well tolerated and may be an important new sleep promoting compound in military operations if further studies warrant.

INTRODUCTION

The pineal hormone melatonin is an important chemical messenger for synchronizing the mammalian circadian system (Armstrong, 1989). Melatonin is the chemical signal of darkness in that the presence of melatonin communicates the nocturnal circadian phase (Reiter, 1991b). Melatonin currently commands growing interest and importance in the scientific, medical, and popular media. This paper presents a brief review of melatonin's neurophysiology and then describes an experiment assessing melatonin's ability to affect diurnal mood.

Within the pinealocytes, melatonin is synthesized from the amino acid tryptophan, which is actively taken up from the blood stream. This synthesis occurs by the hydroxylation and decarboxylation of tryptophan to form serotonin. Serotonin is subsequently N-acetylated by serotonin N-acetyltransferase (SNAT), the rate-limiting step in melatonin synthesis (Klein, 1970; Klein, 1979). This enzyme's activity is increased 30- to 70-fold during darkness, leading to melatonin production almost exclusively at night under normal conditions. The final enzyme in the production pathway is hydroxyindole-O-methyl transferase (HIOMT). HIOMT levels are usually higher at night, but to a lesser extent than SNAT. Wurtman showed the inherent rhythmicity of pineal function in 1963 using serotonin, melatonin, and HIOMT (Wurtman, 1963). This light-dark variation in melatonin synthesis is the essential feature highlighting the central role of the pineal in circadian physiology (Arendt, 1988). High affinity binding sites for melatonin are

present in the adult suprachiasmatic nuclei (SCN), suggesting that melatonin affects the primary circadian oscillator directly (Reppert , 1988).

Melatonin is released from the pinealocytes directly into the cerebral spinal fluid and the blood stream. The stimulus for the nocturnal increase in melatonin synthesis is provided by electrical activity originating in the suprachiasmatic nuclei (SCN). Of primary importance in the generation of the circadian melatonin rhythm is the neural information that arrives at the pinealocytes via postganglionic sympathetic neurons whose cell bodies are in the superior cervical ganglia. The major neurotransmitter within the sympathetic nerve terminals in the pineal is norepinephrine. The release of norepinephrine allows for its interaction with post-synaptic receptors in the pinealocyte membrane (Reiter, 1991c). Since melatonin is highly lipophilic, it easily crosses the blood-brain barrier (Reiter, 1991a). Pervasive melatonin binding sites and receptors have been reported both centrally and peripherally (Stankov, Fraschini, Reiter, 1991; Stankov & Reiter, 1990). Due to its high diffusibility, melatonin can also enter cellular and sub-cellular components (Reiter, 1993).

Studies have shown that the daily administration of melatonin exerts physiologic effects, including feelings of fatigue (Arendt, 1984). It has been found that an acute dose of melatonin (50 mg, p.o.) increased subjective feelings of fatigue when given in the morning, 0900, but not in the evening, 1900 (Nickelsen, 1989).

Dollins noted that melatonin ingestion increased feelings of sleepiness and fatigue at lower, more physiologic doses than previously reported. Dollins and coworkers used oral melatonin doses of 10 mg, 20 mg, 40 mg and 80 mg (Dollins, 1993).

The daytime administration of high levels of exogenous melatonin does not improve nighttime sleep (Anton-Tay, 1971). Exogenous melatonin, administered at night, after the body's own nighttime melatonin secretion has been initiated, does not interfere with normal sleep (James, 1987). James reported an increase in rapid eye movement (REM) latency following nocturnal melatonin administration (5 mg, p.o.) to normal subjects and as little as 1 mg of melatonin, p.o. to insomniacs (James, 1990). Cramer reported shorter sleep latencies in his subjects given melatonin at 2130 hrs. without affecting significantly any other nighttime sleep parameters (Cramer, 1974).

It has been hypothesized that melatonin serves as a signal to the sleep-wake system that it is time to sleep. Administering exogenous melatonin before the endogenous signal has been sent can facilitate the initiation of sleep (Dollins, 1994) while administering exogenous melatonin after the endogenous signal has been sent may have little effect (Ferini-Strambini, 1992). The time of this hypothetical endogenous melatonin signal may be close to the dim light melatonin onset (DLMO) time (Lewy, 1992). The DLMO is used as a circadian reference point, that can reliably assess small changes in circadian phase position. The hypothetical endogenous

melatonin signal may reflect a threshold of circulating melatonin above which sleep is actively facilitated and below which sleep is not actively facilitated.

During nighttime sleep, auditory threshold is inversely associated with body temperature. Waldhauser's studies have shown that exogenous melatonin administration may have reduced the adverse effects of noise by increasing auditory thresholds, especially in the middle part of the night (Waldhauser, 1990). In comparing the sleep architecture of exogenously administered melatonin with that of normal sleep, Cramer has shown that melatonin has little to no effect on sleep architecture (Cramer, 1974). Currently it is hypothesized that the effects of exogenous melatonin at night are most likely due to the pre-existing presence of high levels of endogenous melatonin that are already affecting the sleep-wake system.

Anton-Tay and coworkers reported the first investigation of melatonin's daytime sleep inducing effects in humans (Anton-Tay, 1971). Melatonin had large hypnotic effects compared to placebo seen initially in parieto-occipital EEG deactivation. Melatonin also increased time interval estimates of successive light pulses and slightly increased reaction time. Cramer reported that the intravenous administration of 50 mg of melatonin at 1600 hrs. facilitated polygraphically recorded sleep latency (Cramer, 1974). It has also been shown that the intranasal administration of 1.7 mg of melatonin in the morning will induce sleep onset (Vollrath,

1981). Lieberman used a crossover design and administered 80 mg oral doses of melatonin or placebo at 1200, 1300, and 1400 to 14 male volunteers. He found that compared to placebo, exogenous melatonin decreased oral temperature, and increased subjective self-ratings of fatigue, sleepiness, and confusion (Lieberman, 1984). Melatonin also decreased subjective measures of activity and vigor, slowed reaction times and decreased errors of commission on a four choice reaction time task (Lieberman, 1984). Dollins and coworkers were able to replicate these effects using a single melatonin dose at 1145 of either 10, 20, 40, or 80 mg. All doses of melatonin were found to decrease oral temperature, increase subjective measures of fatigue and sleepiness and decrease subjective self-ratings of vigor and activity (Dollins, 1993). Melatonin also slowed psychomotor reaction times on a four choice task and impaired accuracy on a long-duration (60 minute) auditory vigilance task. This same range of doses administered at 0915 in the morning yielded similar effects. Hughes and coworkers used a placebo controlled, double-blind, crossover design to assess the hypnotic efficacy of 3 doses of exogenously administered melatonin (1, 10, and 40 mg) administered at 1000. All doses of melatonin shortened sleep latency when compared to placebo. The higher doses of melatonin increased sleep duration in a four hour sleep episode (1200-1600). The sleep architecture of melatonin induced naps may be more like physiological nighttime sleep than the placebo naps (Hughes, 1994). Melatonin did not yield anterograde amnesia tested before and after the nap and did not impair performance tested after the nap. MacFarlane noted that the daily administration of

melatonin to humans exerted physiologic effects, including the subjective enhancement of sleep quality (MacFarlane, 1991). From the above studies, it appears that melatonin is safe when administered exogenously and is efficacious in initiating and sustaining sleep. In addition, Lewy has shown that exogenous melatonin administration in humans phase shifts circadian cyclicity according to an established phase-response curve (Lewy, 1992).

Few studies have looked at the effects of melatonin on multiple mood states. Therefore, a high and a low dose of melatonin were compared for effects on mood and temperature in a study of melatonin's ability to affect diurnal mood. A goal of this study was to add further dose information to the growing number of studies showing melatonin's affect on fatigue and body temperature. The study was designed to provide further evidence for melatonin's affect on other mood states. Finally, salivary levels of melatonin were compared with blood plasma levels to determine the efficacy of using salivary melatonin levels as a non-invasive measure of blood plasma melatonin.

METHODS

This study was conducted in four separate testing sessions during June and July of 1992 in a human testing facility at Brooks AFB, TX. The four sessions were spaced from 3 to 8 days apart and a different melatonin was given during each session (100 mg, 10 mg, either 1 mg or 0 mg, and no dose). The six subjects were all healthy, male volunteers, and ranged in age from 20 to 42 years.

These procedures were approved by the Armstrong Laboratory/Brooks AFB Human Use Committee. The subjects were required to refrain from the consumption of alcohol and were to be in bed by 2200 the nights prior to each of the testing sessions. They were to consume no drugs, including acetylsalicylic acid (aspirin), or caffeinated beverages (coffee or tea). The subjects were to eat a light breakfast and be at the testing facility by 0800 on the days of testing. Upon arriving at the testing facility, each subject had an 18 gauge catheter with a heparin lock implanted in a forearm vein for blood sample withdrawal. Each subject had a work station where they could sit and occupy themselves until the time for salivary, serum, mood or temperature samples every hour. They could not sleep during the study.

All six subjects participated in each of the four testing sessions. Subjects were given the assigned dose at 0915 in a double-blind manner, and the capsule was consumed with fruit juice. The doses were randomly assigned for each test session. All subjects received 100 mg and 10 mg doses of melatonin on one of the assigned test days (n=6). Three of the subjects received 1 mg and three received 0 mg of melatonin on an assigned test day. All subjects were again tested on a non-dose day using identical testing procedures (n=6), with the exception that serum was not collected and conditions were not blinded.

Serum samples were obtained from each volunteer through the forearm catheter every even hour starting as soon as the catheter

was in place at 0800, 1000, 1200, 1400, and 1600). Salivary samples were self-obtained using 10 cc syringes to aspirate from the oral cavity approximately 5 cc of saliva. Salivary samples were obtained hourly. The serum and salivary samples were immediately centrifuged at 3,000 rpm for a minimum of ten minutes. The supernatant was pipetted off, placed in labelled tubes and immediately frozen at -70 degrees F. The samples were stored until they could be assayed for melatonin concentration. Guildhay Radioimmunoassay was used to assess the serum and salivary levels of melatonin.

The School of Aerospace Medicine (SAM) Fatigue Scale, oral temperature, and salivary samples were taken every hour (10 readings) whereas the serum samples and the Profile of Mood States (POMS) were taken on the even hours (5 readings). Immediately after the serum samples were obtained, the subjects completed the POMS questionnaire (even hours). The POMS is a self-report scale that consists of 65 adjectives, each of which is rated on a 5 point scale (McNair 1971). Subjects rate how well a given adjective describes their present feelings. The 65 adjectives aggregate into 6 emotional dimensions: Anger, Confusion, Depression, Fatigue, Tension, and Vigor.

The SAM Fatigue Scale is a seven point self-report fatigue scale. The scale ranges from 1 (fully alert; wide awake; extremely peppy) to 7 (completely exhausted; unable to function effectively; ready to drop). This scale has been shown to be sensitive to

fatigue. Oral temperatures were self-obtained hourly using a Becton Dickinson (B-D) Digital Thermometer.

The subjects spent the majority of time between tests playing computer games, which did not change between test sessions. During the testing sessions, subjects were not allowed to consume food or caffeinated beverages. Fruit juices were provided to all subjects during the testing sessions and short (<5 min.) toilet breaks were allowed. The testing room was temperature controlled in a comfortable temperature range from 68 to 72 degrees F., with adequate lighting (approximately 800 lux) for reading, writing, and computer work. Subjects were able to interact with each other and the computer games as desired between testing and survey intervals.

Melatonin was obtained from Sigma Chemical Company, Food and Drug Division. The appropriate dose of melatonin was weighed and mixed with methyl cellulose and placed in standard gelatin capsules each week prior to the study. Gelatin capsules containing 0 mg, 1 mg, 10 mg, and 100 mg of melatonin were stored in separate refrigerated containers, and protected from light and humidity prior to dosing.

ANALYSIS

A within-groups analysis of variance was used to compare dose effects of melatonin on the different measures over time. Subjects receiving the 0 mg capsule (n=3) were used as the placebo condition for the statistical analysis. Data from the non-dosed session,

from the three subjects who did not receive a 0 mg dose of melatonin, were used to complete the data for the 0 mg condition in the analysis (n=6). There were too few observations (n=3) in the 1 mg dosing condition to be considered in the analysis. It was expected that a dose-dependent relationship would be found for temperature and POMS fatigue and vigor measures, but not for other mood measures. One of the subjects was excluded from the analysis due to ill health on two of the three dose days.

RESULTS

Salivary levels of oral melatonin were significantly correlated with serum levels as shown in Figure 1 ($r = 0.74$; $p < 0.0001$). The dark vertical arrow indicates the time of melatonin dosing in all figures (0915). The 100 mg dose for serum and saliva was significantly different from the 10 mg and 0 mg doses ($p < 0.04$ serum; $p < 0.0002$ saliva). However, the 10 mg dose was not significantly different from the 0 mg dose whether melatonin levels were tested in saliva or serum. Figure 1 also shows that serum and saliva levels for 100 mg and 10 mg remained elevated through the duration of the study.

Oral temperature was affected by melatonin in a dose dependent manner, although not significantly. Figure 2 shows the change from 0800 baseline levels for 0 mg, 10 mg, and 100 mg doses. The peak affect on temperature appears to begin 3 hours after dosing and it is maintained for at least 7 hours. SAM Fatigue scores were greatest at 1200, as compared to the 0800, 0900, and 1000 scores

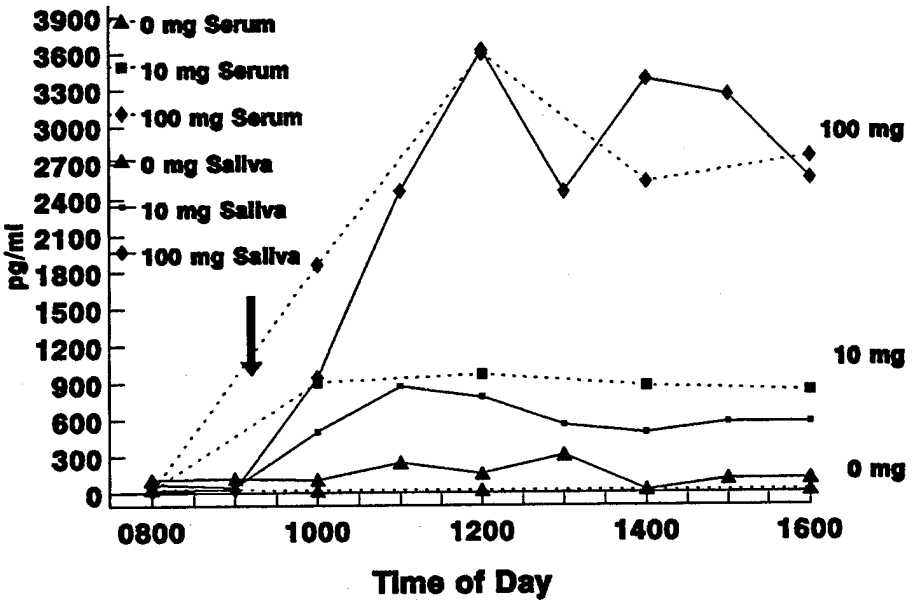

Figure 1

($p < 0.0004$). There was a significant dose by time interaction ($p < 0.0003$).

The 100 mg dose caused a significant increase in the average POMS fatigue score($p < 0.048$) over the 10 mg and 0 mg doses as shown in Figure 3. The 0 mg dose was not different from the 10 mg dose. Like temperature, the time course of this effect peaked 3 hours post dose and extended for about 7 hours.

The average POMS vigor score (Figure 4) was found to vary significantly by time ($p < .0014$). An interaction of dose (100 mg)

Oral Temperature by Dose (Difference From Baseline Value)

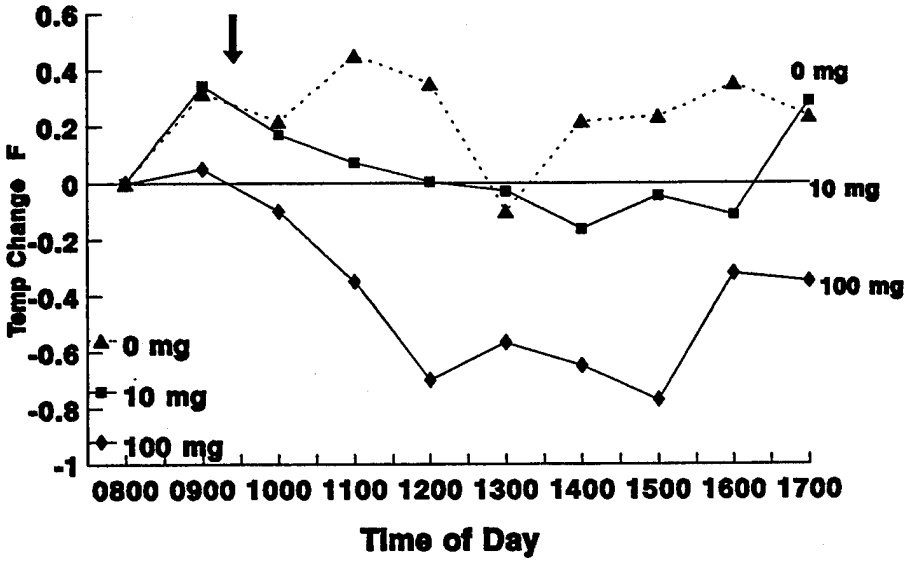

Figure 2

POMS Fatigue by Dose

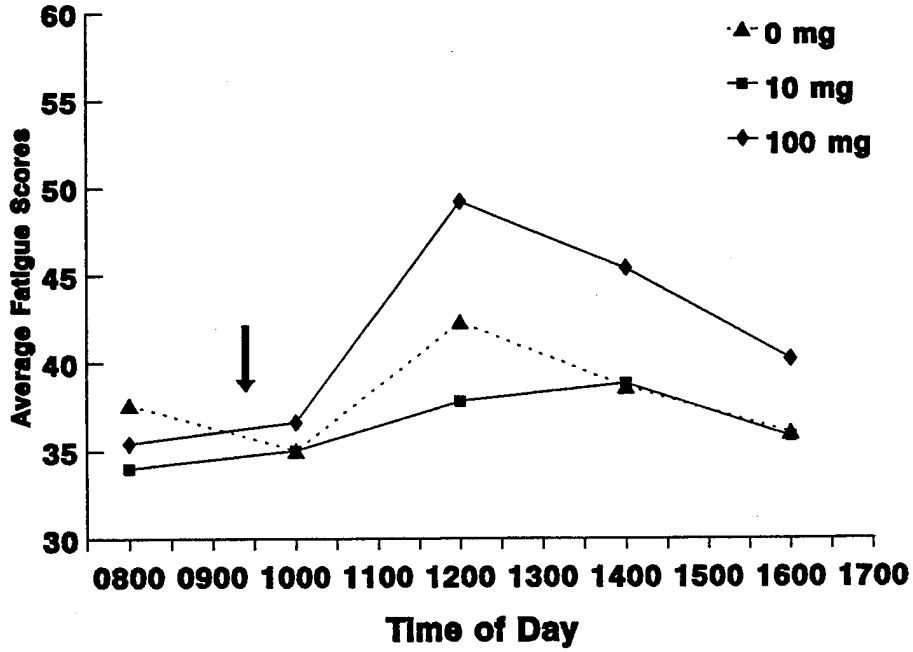

Figure 3

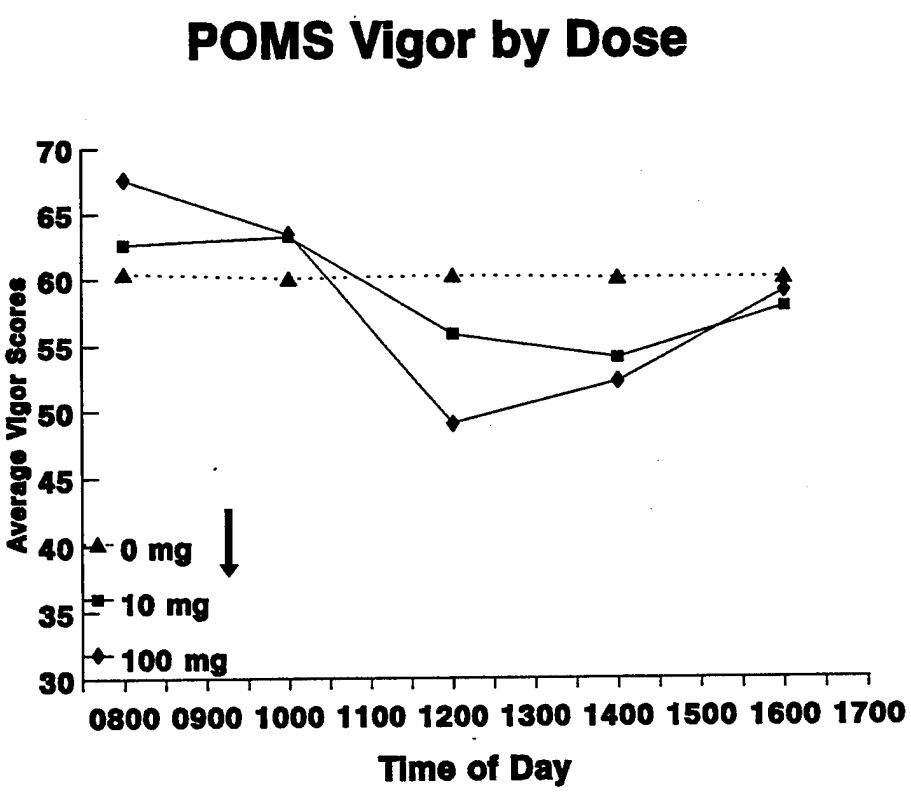

Figure 4

by time (1200 hrs.) was found for POMS vigor ($p < .03$) compared to placebo.

The average POMS confusion score was found to vary significantly by time ($p < 0.0308$) as shown in Figure 5. The 1200 POMS confusion score was significantly greater than the POMS confusion scores noted at 0800, 1000, and 1400.

The significant dose by time interaction for tension scores, as shown in Figure 6, represents an increase over time by the placebo group and does not indicate an effect of melatonin. However the lower tension scores for melatonin compared to placebo may suggest a melatonin effect. POMS anger and depression scores

were unaffected by the melatonin doses used.

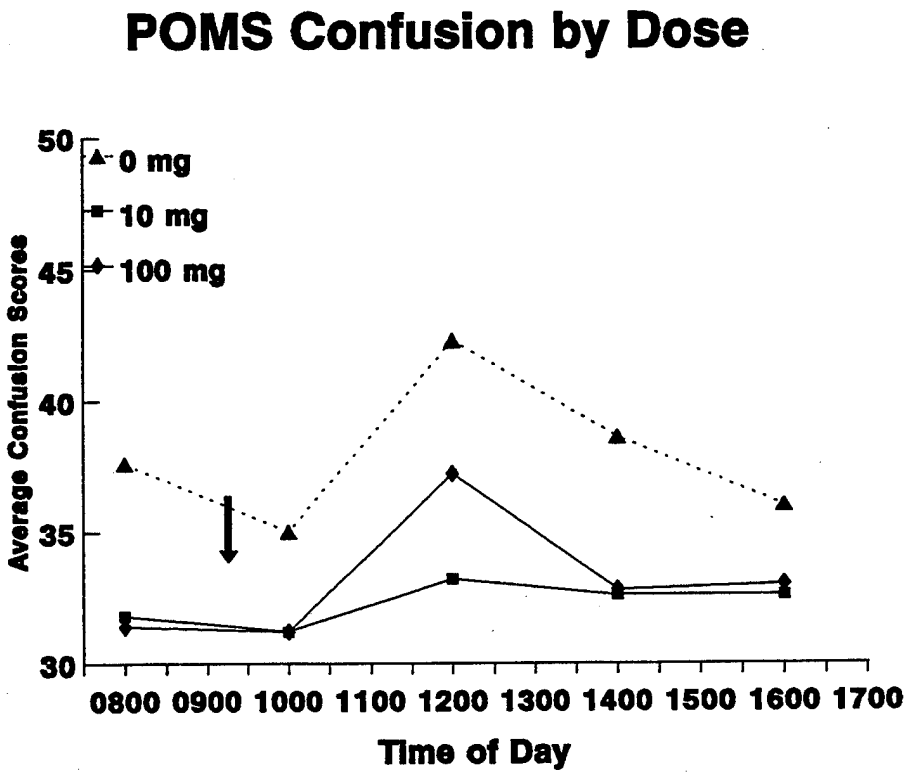

Figure 5

DISCUSSION

These results indicate that ingestion of melatonin (10 and 100 mg) at 0915 resulted in correspondingly increased levels of salivary and serum melatonin. Salivary levels would seem to represent, on average, an accurate and non-invasive estimate of plasma levels. Both the 10 and 100 mg doses decreased oral temperature as compared to placebo, however the results were not statistically significant. The lack of a statistically significant temperature effect was probably due to the small sample size since it has been reported by others (Dollins, 1993). The results of this

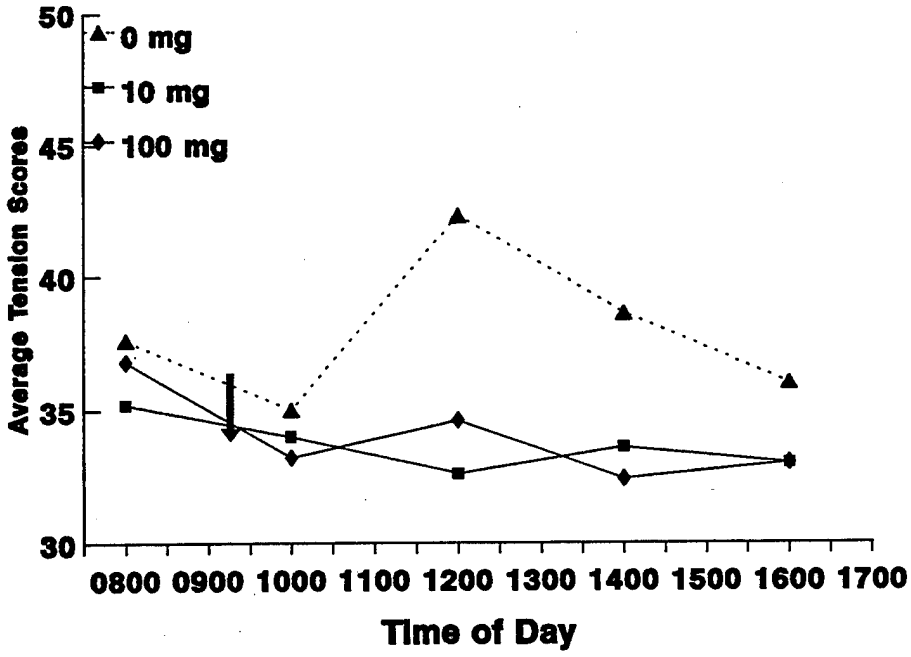

Figure 6

inves-tigation add to the current body of evidence that exogenous melatonin has significant fatiguing qualities. Melatonin produced significant increases in average POMS fatigue scores with both doses as compared to placebo. Both melatonin doses also significantly reduced average POMS vigor scores with time as compared to placebo. Initial vigor scores were greater for the 10 mg and 100 mg conditions prior to receiving melatonin at 0800, as shown in Figure 4. These data suggest that POMS vigor may be more variable than the other POMS dimensions. However, Figure 4 reveals that vigor scores dropped for 100 mg as the fatigue scores were rising (Figure 3). POMS confusion and tension scores were lower for the two melatonin conditions than placebo (Figures 5 and 6). These mood data may reflect a possible anxiolytic effect of melatonin.

The long duration of melatonin's effects found here (7 hours) may be due to the gel caps used. These were noticeably hardened from exposure to humidity and temperature as compared to plastic wrap protected gel caps. This may have slowed the absorption of melatonin. However, it does suggest that more slowly dissolving capsules may extend the benefits of melatonin's effects.

No untoward side effects or adverse reactions to exogenous melatonin were observed throughout the study. The peak in the average POMS confusion score at 1200 hours after the 0915 dose, may be related to the lack of a meal at a normal meal time. The average POMS confusion score reverted to baseline with time for both doses, signifying that this is a temporary effect of melatonin if it is attributable to melatonin at all.

CONCLUSIONS

Future research efforts with melatonin should better assess the pharmacokinetics of exogenous melatonin administration. These studies should also focus on the behavioral and performance decrements associated with daytime melatonin administration. This study was conducted to demonstrate that melatonin can be used as an effective and safe alternative to other agents to induce fatigue and possibly promote daytime sleep. Future research will focus on using daytime melatonin to promote daytime sleep and thereby increase nocturnal performance. Operationally, induction of diurnal fatigue may make melatonin an interesting compound for the flight surgeon when considering ways to promote daytime sleep in

our ever expanding arena of nighttime operations.

REFERENCES:

Anton-Tay F, Diaz JL, Fernandez-Guardiola A. On the effect of melatonin upon human brain: Its possible therapeutic implications. Life Sciences. 1971; 10: 841-850

Arendt J. Melatonin. Clinical Endocrinology. 1988; 29: 205-229

Arendt J, Borbely AA, Franey C, Wright J. The effect of chronic, small doses of melatonin given in the late afternoon on fatigue in man: a preliminary study. Neurosci. Lett. 1984; 45: 317-321

Armstrong SM. Melatonin: The internal zeitgeber of mammals? Pineal Research Reviews. 1989; 7: 157-202

Cramer H, Rudolph J, Consbruch U, Kendel K. On the effects of melatonin on sleep and behavior in man. In Serotonin: new vistas, biochemistry and behavioral and clinical studies (E.Costa Ed.) Advances in Biochemical Psychopharmacology. 1974; 2: 187-191, Raven Press, NY

Dollins AB, Lynch HJ, Wurtman RJ, Dneg MH, Kischka KU, Gleason RE, Lieberman HR. Effect of pharmacologic daytime doses of melatonin on human mood and performance. Psychopharmacology. 1993; 112: 490-496

Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of

inducing nighttime serum melatonin concentrations in daytime sleep, mood, body temperature, and performance. Proceedings of the National Academy of Sciences. 1994; 91: 1824-1828

Ferini-Strambini L, Zucconi M, Biella G, Oldani A, Stankov B, Fraschini F, Smirne S. Sleep Research. 1992

Hughes RJ. Melatonin, body temperature and sleep in humans: a review of a new hypnotic drug. Final Report for Summer Graduate Student Research Program, Armstrong Laboratory. September 1994.

James SP, Mendelson WB, Sack DA, Rosenthal NE, Wehr TA. The effect of melatonin on normal sleep. Neuropsychopharmacology. 1987; 1: 41-44

James SP, Sack DA, Rosenthal NE, Mendelson WB. Melatonin administration in insomnia. Neuropsychopharmacology. 1990; 3: 19-23

Klein DC, Weller JL. Indole metabolism in the pineal gland, a circadian rhythm in N-acetyltransferase. Science. 1970; 169: 1093-1095

Klein DC. Circadian rhythms in the pineal gland. Endocrine Rhythms (D.T. Krieger, ed.) 1979; pp. 203-223, Raven Press, New York

Lewy AJ, Ahmed S, Latham Jackson JM, Sack RL. Melatonin shifts

human circadian rhythms according to a phase-response curve. Chronobiology International. 1992; 9(5): 380-392

Lieberman HR, Waldhauser F, Garfield G, Lynch HJ, Wurtman RJ. Effects of melatonin on human mood and performance. Brain Research. 1984; 323: 201-207

MacFarlane JG, Cleghorn JM, Brown GM, Streiner DL. The effects of exogenous melatonin on the total sleep time and daytime alertness of chronic insomniacs: a preliminary study. Biol. Psychiatry. 1991; 30: 371-376

McNair, D. Profile of Mood States. Educational and Industrial Testing Service. 1971.

Nickelsen T, Demisch L, Demisch K, Radermacher B, Schoffling K. Influence of subchronic intake of melatonin at various times of the day on fatigue and hormonal levels: a placebo-controlled, double-blind trial. J. Pineal Res. 1989; 6: 325-334

Reiter RJ. Melatonin: That ubiquitously acting pineal hormone. News in Physiological Sci. 1991a; 6: 223-227

Reiter RJ. Melatonin: the chemical expression of darkness. Mol & Cel Endocr. 1991b; 79: C153-C158

Reiter RJ. Pineal melatonin: Cell biology of its synthesis and of

its physiological interactions. Endocrine Reviews. 1991c; 12(2): 151-180

Reiter RJ, Poeggeler B, Tan DX, Chen LD, Manchester LC, Guerrero JM. Antioxidant capacity of melatonin; a novel action not requiring a receptor. Neuroendocrinol. Letters. 1993; 15: 103-116

Reppert SM, Weaver DR, Rivkees SA, Stopa EG. Putative melatonin receptors in a human biological clock. Science. 1988; 242: 78-81

Stankov B, Fraschini F, Reiter RJ. Melatonin binding sites in the central nervous system. Brain Research Reviews. 1991; 16: 245-256

Stankov B, Reiter RJ. Melatonin receptors: current status, facts and hypotheses. Life Sciences. 1990; 46: 971-982

Vollrath L, Semm P, Gammel G. Sleep induction by intranasal application of melatonin. Adv. Biosci. 1981; 29: 327-329

Waldhauser F, Saletu B, Trinchard-Lugan I. Sleep laboratory investigations on hypnotic properties of melatonin. Psychopharmacology (Berlin). 1990; 100(2): 222-226

Wurtman RJ, Axelrod J, Phillips LS. Melatonin synthesis in the pineal gland: control by light. Science. 1963; 142: 1071-1073